Using shape effects to target antibody-coated nanoparticles to lung and brain endothelium.

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Public Summary:
The cells that line blood vessels - called the vascular endothelium - offers are targets for the treatment of cancer, cardiovascular diseases, inflammation, and oxidative stress. Significant research has been focused on developing agents to target the endothelium in diseased tissues. This includes identification of antibodies against adhesion molecules and neovascular expression markers or peptides discovered using phage display. Such targeting molecules also have been used to deliver nanoparticles to the endothelium of the diseased tissue. Here we report, based on in vitro and in vivo studies, that the specificity of endothelial targeting can be enhanced further by engineering the shape of ligand-displaying nanoparticles. Experiments in mice confirmed that shape-induced enhancement of vascular targeting is also observed under physiological conditions in lungs and brain for certain nanoparticles. These findings will aid in the development of drugs to fight cancer.

Scientific Abstract:
Vascular endothelium offers a variety of therapeutic targets for the treatment of cancer, cardiovascular diseases, inflammation, and oxidative stress. Significant research has been focused on developing agents to target the endothelium in diseased tissues. This includes identification of antibodies against adhesion molecules and neovascular expression markers or peptides discovered using phage display. Such targeting molecules also have been used to deliver nanoparticles to the endothelium of the diseased tissue. Here we report, based on in vitro and in vivo studies, that the specificity of endothelial targeting can be enhanced further by engineering the shape of ligand-displaying nanoparticles. In vitro studies performed using microfluidic systems that mimic the vasculature (synthetic microvascular networks) showed that rod-shaped nanoparticles exhibit higher specific and lower nonspecific accumulation under flow at the target compared with their spherical counterparts. Mathematical modeling of particle-surface interactions suggests that the higher avidity and specificity of nanorods originate from the balance of polyvalent interactions that favor adhesion and entropic losses as well as shear-induced detachment that reduce binding. In vivo experiments in mice confirmed that shape-induced enhancement of vascular targeting is also observed under physiological conditions in lungs and brain for nanoparticles displaying anti-intracellular adhesion molecule 1 and anti-transferrin receptor antibodies.

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